Chapter

# Menaquinone-7: Wide Ranging Physiological Relevance in Muscle and Nerve Health

*Dilip Mehta, Anselm de Souza and Shashank S. Jadhav*

## Abstract

Menaquinone-7 plays a significant role in cardiovascular and bone health. In recent times there is a growing interest in understanding the role of Menaquinone-7 in health and diseases. Several population-based studies have reported specific health effects of the long-chain menaquinones, notably MK-7, MK-8, and MK-9. There are several epidemiological studies, clinical trials, along with *in vivo* and *in vitro* studies confirming the role of Menaquinone-7 in health and diseases. More recently, research group at Synergia Life Sciences has discovered a wider role for Menaquinone-7 in energy homeostasis ($VO_{2max}$), peripheral neuropathy, muscle cramps and mitochondrial respiration not only through improvement of the electron transport but also the perfusion improving oxygen availability. In the current chapter, the authors have discussed the wider physiological role of Menaquinone-7 highlighting the recent research with Menaquinone-7 in the areas of Muscle and Nerve Health.

**Keywords:** Menaquinone-7, muscle cramps, peripheral neuropathy, bone health, cardiovascular, insulin resistance, deficiency, catabolism, SXR, energy homeostasis

## 1. Introduction

Menaquinone-7 belongs to Vitamin K group. The two general categories of vitamin K are Phylloquinone (Vitamin K1) and Menaquinones, also referred as MK-n (clinical nomenclature Vitamin K2-n) having side chains with 4–12 prenyl units (MK-n where n stands for the number of isoprenoid units, MK-4 to MK-12) 9 (**Figure 1**). Their physiological and patho- physiological roles are specific.

## 2. Biological activity of Menaquinone-7

Vitamin K was discovered by the Danish scientist, Henrik Dam, in the 1930s. Dam's discovery was during his quest to understand chicken's cholesterol metabolism by feeding them a diet free of sterols and low in fat [1]. This reduced their intake of fat-soluble vitamin K, resulting in chickens developing large subcutaneous and intramuscular hemorrhages. This initial finding led to isolating, identifying, and characterizing the structure of vitamin K and its importance as an anti-haemorrhagic agent. Of the many metabolic processes related to vitamin

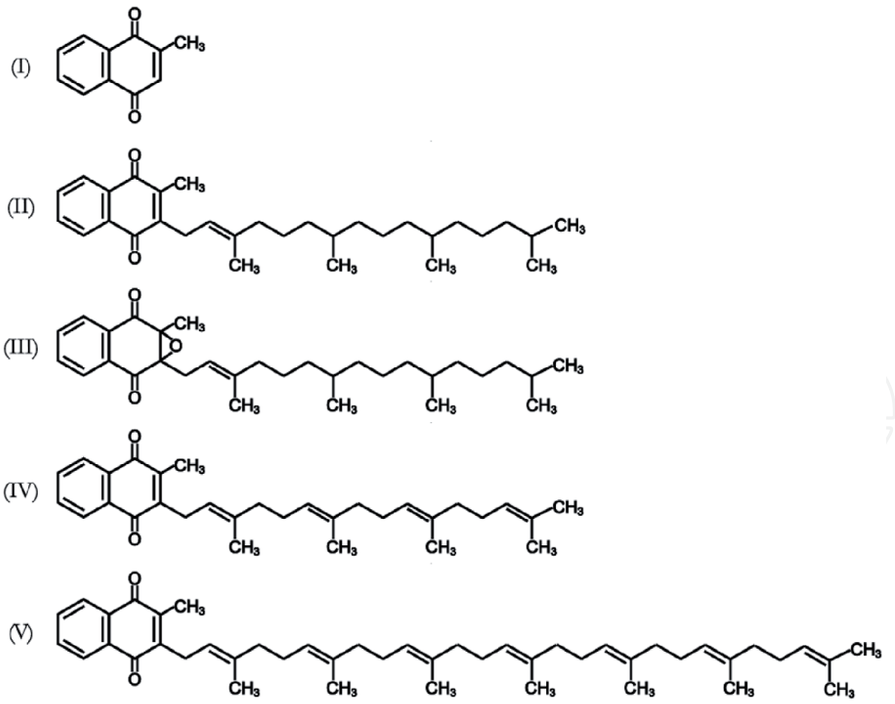


**Figure 1.**
*Chemical structures of various isoforms of Vitamin K. chemical structures of some K vitamins and metabolites. Nomenclature: Chemical name and IUPAC name and abbreviation in brackets: (I) 2-methyl1,4-naphthoquinone (Menadione; K3), (II) 2-methyl3-phytyl-1,4-naphthoquinone (Phylloquinone; K1), (III) 2-methyl-3-phytyl-1,4-naphthoquinone-2,3-epoxide (Phylloquinone epoxide; K1O), (IV) 2-methyl-3-geranyl-geranyl1,4-naphthoquinone (Menaquinone-4; MK-4), (V) 2-methyl-3-farnesylgeranylgeranyl-1,4-naphthoquinone (Menaquinone-7; MK-7).*

K deficiency, bleeding remains the potentially most serious generally known consequence. However, the role of vitamin K's impact on osteoporosis and its inhibitory role in arterial calcification and vascular biology is now recognized in general populations. It is axiomatic that these metabolisms require vitamin K for γ-carboxylation and that this step is essential to their proper functioning. However, there are many other functions of vitamin K recently discovered that seem to be independent of its classical co-factor function. Vitamin K's metabolic effects, e.g., ameliorating effect on peripheral neuropathy, cramps, autonomic nervous system, improving perfusion, etc., remain unexplained. Additionally, vitamin K also acts as a ligand for the receptor SXR, the steroid and xenobiotic sensing nuclear receptor (SXR), which is a transcriptional regulator of the cytochrome P450 gene CYP3A4.

Over the years, the understanding of the vitamin K family has evolved, with the recognition of two primary forms of vitamin K- vitamin K1 (phylloquinone) and vitamin K2 (menaquinones). All K-vitamins have same function, but they exhibit differences in bioavailability and bioactivity. Vitamin K2, the main storage form in animals, has several subtypes, which differ in isoprenoid sidechain length. These vitamin K2 homologs are called menaquinones and are characterized by the number of isoprenoid residues in their side chains. Menaquinones are abbreviated as MK-n, where M stands for menaquinone, the K stands for vitamin K, and the n signifies the number of isoprenoid side chain residues. MK-4 and MK-7 are the two prominent menaquinones in human nutrition. MK-7 and other long-chain menaquinones are different from MK-4 in that they are not produced by human tissue but are generated by bacteria in the gut. The available information suggests that a range of vitamin K2 analogues are present as a mixture in several foods, e.g., in sauerkraut, hard cheese, soft cheese and curd cheese [2]. These foods have a long history of consumption by humans as basic foods.

Diet (Natto and cheeses) rich in menaquinones (primarily MK-7) is safe and requires no systemic validation for toxicity. However, because of the role of vitamin K (K1 and K2) in blood coagulation and potential health benefits, there has been considerable effort to elucidate the mechanism of action of menaquinones, primarily MK-7. There is no known toxicity associated with high doses (dietary or supplemental) of the phylloquinone (vitamin K1) or menaquinones (vitamin K2) forms of vitamin K. In several human studies, Natto food, known to contain MK-7, has been investigated for its health benefits.

## 3. Menaquinone-7 safety

The adverse effects of menaquinones, including Menaquinone-7 has been investigated in several animal and *in vitro* toxicity studies. Findings from animal studies for acute, chronic, and genotoxicity and *in vitro* studies for mutagenicity and carcinogenicity showed no significant risks associated with exposure to menaquinones [3]. The absence of adverse effects or death suggest that the minimum lethal dose of Menaquinone-7 is greater than 2000 mg/kg bw [4].

The European Union has permitted the use of Menaquinone-7 as a source of vitamin K for nutritional purposes in foodstuffs. The European Food Safety Authority (EFSA, 2008) [5] examined the safety of Menaquinone-7. The chemistry, nomenclature, dietary sources, intake levels, and pharmacokinetics of menaquinones, and data of nonclinical toxicity and on clinical outcomes related to safety (adverse events) was extensively reviewed by US Pharmacopeia Convention [6] and by the Institute of Medicine (IOM, 2000). The report considers menaquinone as an active form of vitamin K [7].

## 4. Menaquinone-7 in diet

Schurgers et al. [2] have studied levels of Menaquinone-7 in many food products globally and found that the Menaquinone-7 levels are quite negligible in all the food products except Natto, a staple food in Eastern Japan which contains almost 998 mcg of Menaquinone-7 per 100 gm of Natto. The investigators also found small amounts of Menaquinone-7 in natural cheese. Researchers at Synergia Life Sciences have undertaken a study where a number of Indian food products were examined for the levels of Menaquinone-7. The foods tested had particularly included fermented foods consumed by Indians at large. It was observed that the regularly consumed food including fermented foods lack in Menaquinone-7. So, it can be said that Menaquinone-7 is negligible in Indian diet.

The only rich source of Menaquinone-7 is Natto which contains early 900 mcg of Menaquinone-7 in 100 gm's breakfast [2, 8] and different types of cheese [9] though in small amounts. The various common 18 varieties of Dutch cheeses and 13 varieties of European cheeses contain approximately on an average 1.14 and 1.36 mcg Menaquinone-7 per 100 gm of cheese respectively [9]. The hard cheese, soft cheese and curd cheese from Netherlands contains approximately 1.3, 0.5 and 0.3 mcg Menaquinone-7 per 100 gm cheese respectively [2]. Processed cheese from Japan reported 0.3 mcg Menaquinone-7 per 100 gm cheese [10].

Serum concentrations of Menaquinone-7 are higher in frequent natto eaters. Natto is a popular breakfast item used more widely in win Eastern Japan, as compared to Western Japan. The study by Kaneki *et al*. reports an average serum Menaquinone-7 concentration of 5.26 ng/ml in Eastern Japanese women (Tokyo), 1.22 ng/ml in the Western Japanese women (Hiroshima) and 0.37 ng/ml in British

women (London) [11]. The serum concentrations in British women are negligible since they do not consume Natto, but their diet may include cheese which contributes to the small amounts of Menaquinone-7 in their serum.

Globally speaking Menaquinone-7 is negligible in diet. It is true that many bacteria that populate microbiota of the human intestine synthesize Menaquinones. However, it is realized that in the small intestine bacterial growth availing Menaquinone-7 is limited by the rapid transit times. Most synthesis of Menaquinones occur in the large intestine. Shearer *et al*. [12] and Suttie *et al*. [13] have examined the evidence of the contribution of gut menaquinones and concluded that while they do contribute to the human nutrition but not significantly. Karl JP *et al*. have shown that total Menaquinone (Menaquinone-4 to Menaquinone-13) concentration in human gut is highly variable. They measured total daily excretion of menaquinones in feces. The median total daily excretion of menaquinones in feces was 850 nmol/d but was highly variable (Range: 64–5358 nmol/day) [14].

## 5. Role of Menaquinone-7 in various diseases

### 5.1 Cardiovascular diseases

Geleijnse et al. [15] studied 4807 men and women of aged 55 yrs. for 10 years to assess the association of dietary intake of K1 and K2 with aortic calcification, CVD, and total mortality. They concluded that "When consuming daily 45 mcg dietary K2, you have: 50% reduction of arterial calcification, 50% reduction of cardiovascular death, 25 % reduction of all-cause mortality as compared to low intake of dietary K2!"

Gast et al. [16] studied 16,057 women, aged 49–70 years and free of cardiovascular diseases (at baseline) for 8.1 ± 1.6 years. The intake of vitamin K1 was 211.7 ± 100.3 mcg/d and of vitamin K2 intake was 29.1 ± 12.8 mcg/d. They concluded that there is inverse association of vitamin K2 with CHD with reduction of 9.1% per 10 mcg/day. They also found out that vitamin K1 is not related to CHD.

The publication of the above two epidemiological studies, viz. Geleijnse *et al*. and Gast *et al*. Study, has expanded interest the investigations of various beneficial health effects of Menaquinone-7.

### 5.2 Bone health

Knapen *et al*. [17] investigated the effects of low-dose Menaquinone-7 on bone health in healthy postmenopausal women. Menaquinone-7 intake significantly improved vitamin K status and decreased the age-related decline in Bone Mineral Content (BMC) and Bone Mineral Density (BMD) at the lumbar spine and femoral neck. In another placebo-controlled study, the authors investigated the effect of Menaquinone-7 on BMD and found out that Menaquinone-7 preserves trabecular bone structure at the tibia along with decrease in undercarboxylated osteocalcin (ucOC) [18]. In another clinical study Kanellakis *et al*. [19] assessed the effect of dairy products enriched with calcium, vitamin D3, and Menaquinone-7 on parameters of bone metabolism in postmenopausal women following a 12-month intervention. The study revealed more favorable changes in bone metabolism and bone mass indices for the Vitamin K2 supplemented groups. Van Summeran *et al*. [20] studied the effect of 45 mcg Menaquinone-7 on the circulating levels of undercarboxylated osteocalcin (ucOC) and carboxylated osteocalcin (cOC) along with Menaquinone-7 levels in healthy prepubertal children. They showed that the

levels of Menaquinone-7 increased with the supplementation of Menaquinone-7 as compared to baseline levels.

Spronk HMH *et al*. in 2003 conducted an *in vivo* study for assessing tissue specific utilization of Vitamin K2 which resulted in prevention of arterial calcification in warfarin-treated rats. It was shown that the utilization of Vitamin K2 was more efficient in the aorta as compared to other tissues [21].

In a study by Yamaguchi *et al*., the authors have shown the anabolic effect of Menaquinone-7 on bone tissue and osteoblastic MC3T3-E1 cells *in vitro* [22]. Min Zhu *et al*. have shown that Menaquinone-7 has a stimulatory effect on bone tissue and osteoblastic SAOS-2 cells *in vitro* [23]. These studies suggest the role of Menaquinone-7 in osteoblastic bone formation. Recently, it has also been shown that Menaquinone-7 protects osteoblasts from oxidative stress and has beneficial effects on proliferation, differentiation, and mineralization of osteoblasts [24].

### 5.3 Insulin resistance

A decade-long study of 38,094 Dutch males and females aged 20–70 found that the quartile of participants who consumed the most dietary Vitamin K were 20% less likely to develop type 2 diabetes than the quartile with the lowest intake of Vitamin K [25]. Vitamin K2 is linked to lowered risk of developing type 2 diabetes and also a stronger relationship exists for Vitamin K2 intake. The risk of developing type 2 diabetes drops for every 10 mcg (0.01 mg) increase in Vitamin K2 intake. In this study participants with the highest intake of K2 consumed 250–360 mcg (0.25–0.36 mg)/day. Thus, higher intake of Vitamin K2 is linked to lower diabetes risk.

In an attempt to better understand how Vitamin K2 improves insulin sensitivity, researchers from S. Korea studied 42 healthy male volunteers. Participants were either given 30 mg (30,000 mcg) of Vitamin K2 or a placebo each day for 4 weeks. Vitamin K2 supplementation significantly increased insulin sensitivity and seemed to be related to increased carboxylation (activation) of osteocalcin. Researchers concluded that Vitamin K2 can help regulate glucose metabolism by activating osteocalcin, an endocrine hormone that increases insulin sensitivity in humans [26].

Research has shown that for elderly men Vitamin K slows the development of insulin resistance [27]. The researchers concluded that Vitamin K2 plays a potentially beneficial role in reducing the progression of insulin resistance amongst elderly men.

## 6. Recent research

### 6.1 Energy homeostasis ($VO_{2max}$)

In a recent randomized controlled trial, McFarlin et al. investigated the effects of dietary supplementation of Menaquinone-7 on cardiovascular responses to a graded cycle ergometer test. Menaquinone-7 supplementation was associated with a 12% increase in maximal cardiac output, with a trend toward an increase in heart-rate AUC. No significant changes occurred in stroke volume [28]. **Figure 2** demonstrates that Menaquinone-7 treatment was associated with increased cardiac output, stroke volume, heart rate, and decreased blood lactate. Overall, these changes are consistent with increase maximal cardiovascular performance with oral Menaquinone-7 supplementation.

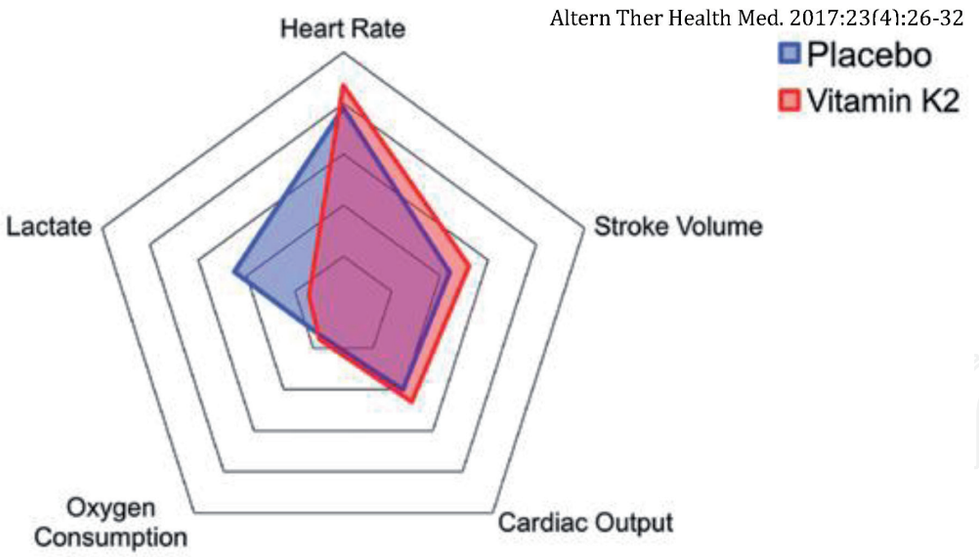


**Figure 2.**
*To visualize the 5 outcome variables (heart rate, stroke volume, cardiac output, oxygen consumption, and blood lactate) on the same scale all data maximal response data after 8 weeks of treatment with either a vitamin K2 (red) or control (rice flour; blue) were normalized using a Log10 adjustment. Plotted values represent increments of a Log10 scale consuming a specific supplement.*

## 6.2 Mitochondrial respiration

Synergia research group has identified Menaquinone-7's pivotal role in mitochondrial ATP generation by acting as a mitochondrial electron transport carrier, thus participating in the energy cycle of the cell. In human cell experiments, it has been shown that the cells' maximum capacity to generate energy, defined as the reserve energy, increases by 30–40% with Menaquinone-7, thus, identifying the role of Menaquinone-7 in redox cycle by transporting electrons in electron transport chain and also mitochondrial generation of ATP (**Figure 3**). This dual role of Menaquinone-7 is especially important to the aging geriatric population and athletes in their need of a greater oxygen supply for the oxidative phosphorylation.

In another *in vitro* study, Menaquinone-7 rescued mitochondrial defects in numerous conditions that affect mitochondrial function. Menaquinone-7 was also effective at improving systemic locomotion defects in fully developed adult pink1 and parkin mutant flies. Menaquinone-7 did not affect mitochondrial remodeling

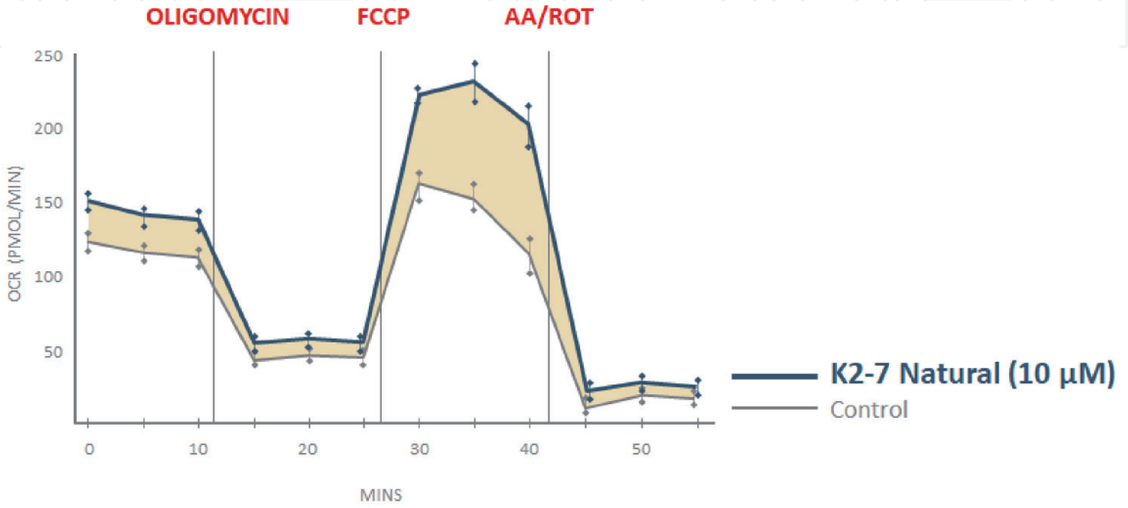


**Figure 3.**
*Mitochondrial respiration: Test sequence in sea horse XF-96 platform.*

directly, but by increasing Electron Transfer Chain efficiency, it contributed to the proton motif force that facilitates ATP production. Menaquinone-7 may thus constitute a promising compound to treat mitochondrial pathology, also in Parkinson's disease (PD) patients suffering from Pink1 or Parkin deficiency [29]. A clinical study has been proposed to investigate the potential effects of Menaquinone-7 in genetically determined PD with mitochondrial dysfunction [30].

### 6.3 Anti-inflammatory

Chronic inflammation is considered an underlying pathology of many diseases that remain poorly understood and treated. Several important chronic diseases with an inflammatory background have been associated with vitamin K deficiency. These include cystic fibrosis, inflammatory bowel disease, pancreatitis, chronic kidney disease and osteoporosis [31, 32]. Circulatory markers of low-grade inflammation such as tumor necrosis factor-alpha (TNF-α), interleukin-1 alpha (IL-1α), and interleukin-1 beta (IL-1β) positively correlate with endothelial damage, atheroma formation, cardiovascular disease, and aging. Menaquinone-7 can modulate immune and inflammatory reactions in the dose–response inhibition of TNF-α, IL-1α, and IL-1β gene expression and protein production [33]. These findings highlight the anti-inflammatory properties of Menaquinone-7, elucidating the anti-inflammatory mechanism of Menaquinone-7 and in establishing the potential biomarker targets in clinical testing of the role of Menaquinone-7 in cardiovascular health as well as other chronic degenerative conditions.

### 6.4 Muscle health

Vitamin K deficiency impacts neuromuscular and vascular function, thus affecting the physical functioning. Vitamin K has a function in promoting vascular smooth muscle differentiation [34]. As disabilities in patients are directly related to muscle strength and physical performance, therefore it is crucial to focus on muscle strength and performance rather than muscle mass [35].

Handgrip indicates muscle strength and is directly related to lower-extremity strength. Calf circumference indicates skeletal muscle mass and is associated with higher strength [36, 37]. A longitudinal cohort study conducted in community-dwelling adults (n: 633, aged: 55–65 years) analyzed the association between vitamin K status and physical functioning over 13 years. An association of low vitamin K status with lower handgrip strength, smaller calf circumference was observed. Low vitamin status in women indicated an existence of association of low vitamin status with poorer functional performance score [38].

Some observational studies conducted in sarcopenia patients showed an association of high vitamin K status in plasma with muscle strength, large muscle mass, and high physical performance.

Thus, it was concluded that physical performance scores rather than muscle mass indicated the beneficial effect of vitamin K on muscle quality [35].

Systremma or leg cramps is a common and distressing problem characterized by involuntary, painful, sudden contractions of the skeletal muscles. It has affecting 30% of people who are over sixty-year-of age and 50% of people over eighty years of age [39, 40]. Muscle cramps may occur in normal subjects during a strong voluntary contraction, sleep, sports or pregnancy but it can also occur due to several pathological conditions such as myopathies, neuropathies, motoneuron diseases, metabolic disorders, hydroelectrolyte imbalances or endocrine pathologies, cirrhosis of liver, in patients on dialysis or may be triggered by intake of certain drugs such

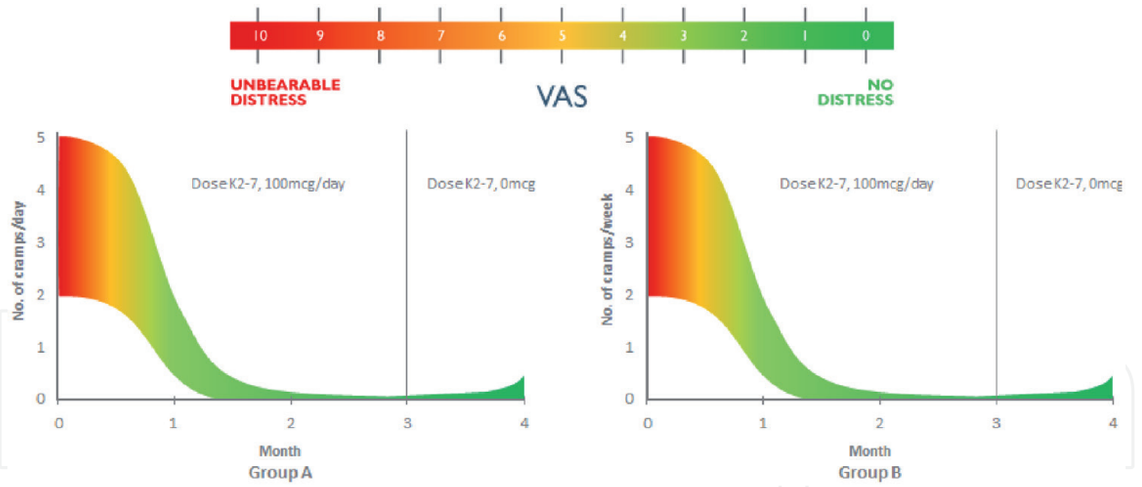


**Figure 4.**
*Decrease in mean severity of cramps as noted on VAS score in both the groups which were divided depending upon the frequency of cramps viz., cramps every day in group A and 2–3 cramps every week in group B.*

as diuretics, laxatives, beta2-agonists, cimetidine, and phenothiazines. Treatment of the underlying cause could successfully relieve this symptom [41, 42].

Diverse causes of muscle cramps has led to varied treatment modalities in clinical practice with varying degree of success in relieving the symptoms [43, 44]. These modalities include quinine Sulphate [45], calcium channel blockers [46], magnesium [47], gabapentin [48], botulinum toxin [49], phenytoin [50], Vit E [51], carisoprodol and orphenadrine [52]. Although quinine is the most used treatment modality in this condition [41], it is associated with several side effects like arrhythmia, tinnitus, headache, nausea, tremor, hypotension, and gastrointestinal upset, and occasionally, potentially fatal hypersensitivity reactions and thrombocytopenia [40, 41]. Due to severe toxicity encountered, US FDA has banned over-the-counter quinine-based products used for leg cramps [41, 53, 54]. This has generated a need for alternative therapeutic agents.

A preliminary open labeled observational study conducted by Vaidya *et al*. showed that daily administration of 100 mcg of Menaquinone-7 for 3 months was associated with a reduction in the frequency, intensity, and duration of idiopathic muscle cramps [55]. Menaquinone-7 at a dose of 100 mcg /day for 3 months was found to be well tolerated and safe and resulted in therapeutic relief of muscle cramps (**Figure 4**).

A research done by Mehta and Vaidya showed that daily administration of vitamin K relieves muscle cramps and prevents its recurrence. Vitamin MK-7 has longer half-life which facilitates its further utilization as it stays in the body for a longer duration. Vitamin K is a safe prophylactic for muscle cramps. Vitamin K also improves the muscle strength evident by relief of fatigue. The inventors have discovered relief from cramps when sufficient dose of vitamin K was administered systematically daily once or more. The preferred range was 10 μg to 1000 μg per day, and the preferred vitamin K was vitamin MK-7 [56].

### 6.5 Nerve health

Peripheral neuropathy (PN) also known as distal symmetric neuropathy or sensorimotor neuropathy, is a common problem with multifactorial aetiologies. Diabetes mellitus is the most common etiology of PN. Neural signals from sensory receptors in the cellular pathway of the peripheral nervous system are damaged in PN. It is a neurological complication where the nerves carrying sensory neurons

from different parts of the body to the central nervous system are denervated hence causing numbness, tingling, motor paralysis and gland or organ dysfunction. PN is a disease with vast spectrum, found in a variety of groups of populations, commonly observed in geriatrics, obese and diabetic population [57].

An epidemiological study conducted by Martyn *et al*. has stated the worldwide prevalence of PN to be around 2.4% which is considerably increasing to 8% in patients older than 55 years [58].

Indian population is susceptible to PN due to large population density, exposed to different adverse environments for a living [59]. Amongst diabetic Indian population, prevalence of neuropathy has been 26–31% [60–62]. In an Indian epidemiological survey conducted amongst about 40 million diabetics in India, at least 10.4 million diabetics showed the symptoms of PN [63].

Some patients with neuropathy may experience extremely painful symptoms, whereas others may have objectively marked neurological deficit without significant painful neurological symptoms [64].

A systematic review analyzing the data of several studies stated that painful diabetic PN occurs in about one in six people with diabetes, impairing the quality of life of people and increasing healthcare cost. Although guidelines have suggested several treatment related recommendations, but they are associated with adjuvant side effects [65]. The risk of developing PN increases with the duration of diabetes and deteriorating glycemic control [64].

Neuropathy is a devastating event in patients with myeloma. Prolonged treatment of Multiple Myeloma (MM) related drugs leads to development of PN in 70% of patients [66]. Neuropathic events in such patients leads to dose reduction of the primary agents (Bortezomib, Thalidomide and Lenalidomide) or reduction in frequency of the therapy. This could further lead to discontinuation of therapy by some of the patients. Therefore, neuropathy in MM needs to be addressed.

The etiopathology of PN is poorly understood. Many factors, including dietary deficiencies, may contribute to the clinical manifestation of the condition [67].

The neurologic manifestations of folate deficiency overlap with those of vitamin B12 deficiency and include cognitive impairment, dementia, depression and commonly PN [64].

Myelopathy with or without an associated neuropathy is the commonly recognized neurological manifestations of vitamin B12 deficiency [68]. Methyl cobalamin is a vitamin B12 analogue, necessary for the maintenance of the nervous system [69]. The diagnosis of neuropathy due to B12 vitamin deficiency remains a real challenge for the clinician [70].

The etiology of diabetic neuropathy has been a debatable topic however, neuropathy due to an inflammatory autoimmune condition that damages the myelin sheet of peripheral nerves and role of menaquinone-7 deficiency in alleviating this condition are considered as the evolving possibilities for diabetic neuropathy.

Vitamin K is considered to have a role in myelin synthesis and repair in central and peripheral nervous systems. Myelin is a sphingolipid, a group of complex lipids which are found in all mammalian cells as a major components of cell membranes, present particularly in high concentrations in cells of the central and peripheral nervous systems [71]. Certain sphingolipids found in the central and peripheral nervous systems have shown a high correlation with the tissue levels of vitamin K. Initially recognized for their structural role, sphingolipids are now considered as the key players in major cellular events such as proliferation, differentiation, senescence, cell–cell interaction, and transformation [72]. Furthermore, several recent research have shown a corelation of alterations in sphingolipids metabolism with aging process [73] and neurodegenerative disorders such as Alzheimer's disease (AD) and Parkinson's disease [52, 74].

Scientific legacy of Meir Lev's group depicted the role for vitamin K in sphingolipid metabolism in a report published in Nature in 1958 [75]. The report showed that Vitamin K serves as a growth factor for the rumen strain *Bacteroides melaninogenicus* (also known as *Fusiformis nigrescens*), which was later found to be linked to cell membrane homeostasis. When *Bacteroides melaninogenicus* was cultured in a medium without vitamin K, cells grew as filaments (i.e., elongated cells), were more fragile when subjected to shaking with glass beads and tended to auto-agglutinate when placed in buffer. Growth of bacteria under such condition was also greatly affected. Vitamin K deficient cultures yielding around 80% lower bacteria weight than those grown from vitamin K replete conditions [76]. Two other reports also explained the role of vitamin K at the membrane level. The reports showed the essential requirement of vitamin K for sphingolipid synthesis. Recent published studies that confirm the modulation of brain sphingolipids by vitamin K nutritional status, underscore the potentially far-reaching effect of vitamin K in brain function given the key role of these lipids in cell-signaling functions.

In the nervous system, vitamin K activates the carboxylation and activation of Gla residues on GAS6 protein (growth arrest-specific gene 6 protein) which is structurally related to another vitamin K-dependent protein (VKDP), anticoagulation factor protein S [77]. GAS6 and related S protein bind and activate the receptor tyrosine kinases of the Tyro3, Axl, and Mer (TAM) family. They are responsible for cell signaling which stimulates the generation of central nervous system repair cells (oligodendrocytes) and increased myelin production including repair after myelin injury (demyelinating injury) [78]. Vitamin K may also act in the central nervous system independent to its role in the carboxylation reaction [79]. Vitamin K independent of VKDP, activates enzyme 3-ketodihydrosphingosine (3-KDS), involved in sphingolipid synthesis which is critical for healthy myelin [80].

Sakaue M et al. investigated the protective effects of different forms of Vitamin K (Vitamin K1 and Vitamin K2–4) in an *in vitro* experiment conducted in primary cultured neurons from cerebella of rat pups where methylmercury-induced the cell death. They also investigated its protective effect against GSH-depletion-induced cell death by employing two intracellular glutathione (GSH) reducers, L-buthionine sulfoximine (BSO) and diethyl maleate (DEM), in primary cultured neurons and human neuroblastoma IMR-32 cells. It was observed that all the forms of Vitamin K inhibited the death of the primary cultured neurons indicating that vitamin K forms have the potential to protect neurons against cytotoxic methylmercury and agents that deplete GSH, without increasing intracellular GSH levels [81]. Kenji Onodera et al. while examining the antinociceptive effects of Vitamin K2–4 in diabetic mice found that no significant difference exist between non-diabetic and diabetic mice in the Vitamin K2–4 induced changes in the nociceptive threshold. This indicated the therapeutic effectiveness of Vitamin K2–4 for treating painful diabetic neuropathy [82].

A serendipitous discovery by two researchers, Mehta and Vaidya is that Menaquinone-7 relieves idiopathic muscle cramps as well as symptoms of diabetic neuropathy. PCT/IN2008/000465, application further claims the safety of usage of Menaquinone-7 in the various novel conditions like neuropathy [56].

In an open labeled study conducted by Kulkarni et al., it was shown that Menaquinone-7 at a dose of 100 mcg twice a day for 8 weeks (**Figure 5**) was well tolerated and safe with a therapeutic activity for the symptoms of peripheral neuropathy [83].

Based on the results of these studies, the next study which is a follow-up study in a larger cohort (n = 100) was planned to address the peripheral neuropathy experienced by patients. Menaquinone-7 capsules (100 mcg / capsule, twice a day) were given orally for 8 weeks and were followed up to 12 weeks. By twelfth week, the score was reduced in megaloblastic anemia as well as in diabetes mellitus groups to

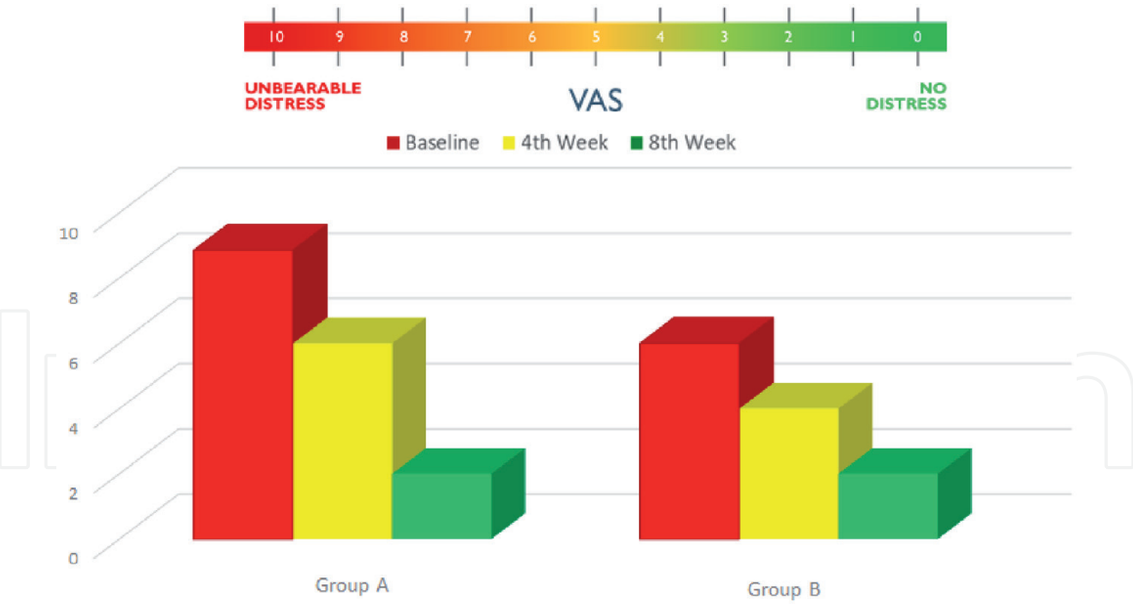


**Figure 5.**
*Decrease in the intensity and severity of PN from baseline to 8th week as noted on VAS score in the groups a and B, where group A (severe) had a VAS score of 8–9 and group B (moderate) with a score of 6–8 at baseline.*

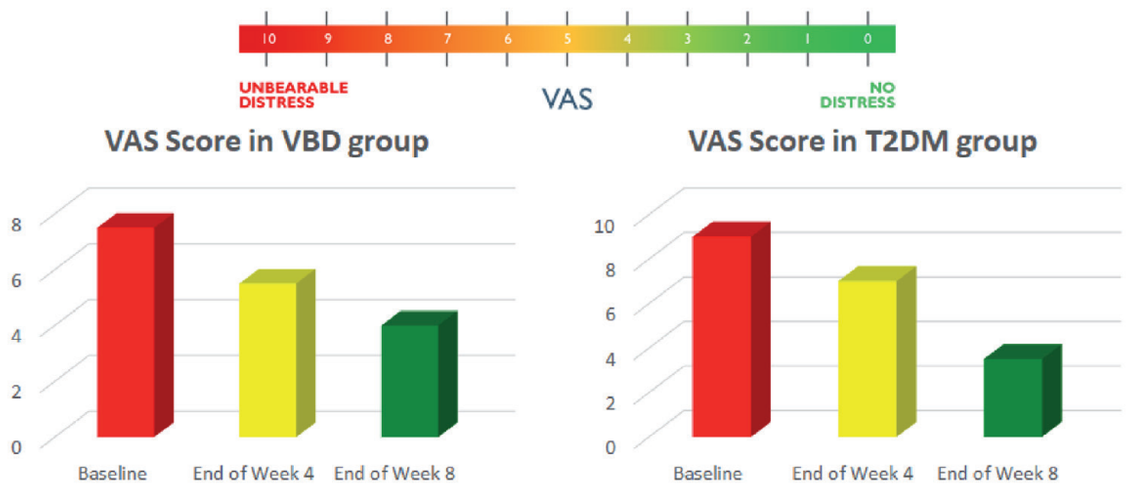


**Figure 6.**
*Decrease in the intensity and severity of PN from baseline to 8th week as noted on VAS score in the groups VBD (Vitamin B12 deficiency) and T2DM (type 2 diabetes mellitus).*

1–2 (**Figure 6**). The decrease was statistically significant ($P < 0.0001$). The tingling and numbness had reduced significantly. There was a significant decrease in the weakness and fatigue [84].

Recently a double-blind placebo-controlled efficacy and safety study of Menaquinone-7 was conducted in 60 patients presenting with peripheral neuropathy and suffering from either vitamin B12 deficiency and/ or type 2 diabetes mellitus. Patients from both the groups' i.e., Vitamin B12 deficiency and type 2 diabetes mellitus had overall VAS score of 9 at baseline. By the end of the twelfth week, patients who were receiving Menaquinone-7 showed statistically significant reduction in the VAS score in Vitamin B12 deficiency as well as in type 2 diabetes mellitus to 2; whereas the patients who were taking placebo in Vitamin B12 deficiency group had reduced to 8, and in type 2 diabetes mellitus group to 9. This study was again performed with same protocol along with estimation of serum Menaquinone-7 levels in serum in a small sample size. The VAS score showed an inverse relationship between Menaquinone-7 levels and peripheral neuropathy symptoms (**Figure 7**) [85, 86].

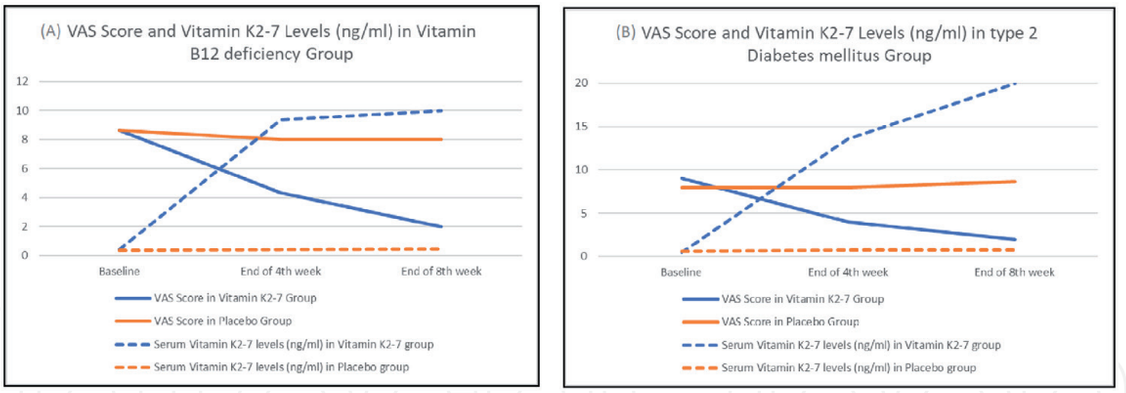


**Figure 7.**
*Average VAS score and serum Vitamin K2–7 levels (ng/ml) in Vitamin B12 deficiency group (A) and type 2 diabetes mellitus group (B).*

Antineoplastic agents are the chemotherapy drugs used for cancer. Chemotherapy-induced peripheral neuropathy (CIPN) is one of the most frequent side effects caused by antineoplastic agents having a prevalence ranging from 19% to over 85%. CIPN is a mostly sensory neuropathy and is associated with motor and autonomic changes of varying intensity and duration [87]. Chemotherapeutics induces toxicity in peripheral nervous system. Oxaliplatin, an antineoplastic agent damages the blood brain barrier (BBB). The possible mechanisms of BBB damage may include proinflammatory cytokines, ROS, or other neurotransmitters, all of which are involved in the peripheral nervous system toxicity induced by chemotherapeutics [88, 89]. The study of Sanna et al. has shown a direct correlation between structural changes in the central nervous system and chemotherapy-induced neurotoxicity [90].

An open labeled observational study to evaluate the iatrogenic neuropathy and its amelioration using Menaquinone-7 in patients with Multiple Myeloma with drug induced PN suggests for the first time that Menaquinone-7 has an ameliorative potential for relief of iatrogenic PN in Multiple Myeloma patients. Menaquinone-7 reduces the symptoms of PN like tingling, numbness, burning sensation, pain, causalgia, wooly feeling, and cramps caused during treatment of MM, thus Menaquinone-7 is found to be useful in the treatment of PN caused due to the therapy of MM [91].

Multiple myeloma (MM) is a type of hematological cancer which is characterized by excessive production of malignant plasma cell clones in the bone marrow [92]. Incidence of iatrogenic PN has been observed in patients with MM who received chemotherapy. It is primarily of a sensory or sensorimotor nature, and the symptoms of tingling, numbness, burning sensation and pain are predominantly bilaterally symmetric [93]. Development of debilitating drug induced PN is one of the major challenges in the treatment of MM, affecting compliance leading to discontinuation of therapy or dose/drug modification [94]. Thus, there is a need of any modality that could reduce the severity and allows continuation of effective therapy in the clinical setting. This preliminary observational study is the first study revealing the potential of Menaquinone-7 in relieving the symptoms of iatrogenic PN in MM patients.

## 7. Conclusion

Menaquinone-7 appears promising in the areas of chronic degenerative conditions such as bone health, cardiovascular, diabetes, energy metabolism, peripheral neuropathy, cramps etc. Newer research is ongoing to confirm its role in many other

areas including immunity, cognition, cancer etc. With the recent discovery of its many biological functions, Menaquinone-7 is sometimes referred to as a multitasking vitamin. Globally speaking Menaquinone-7 is negligible in diet consumed by the population all around the world except in small pockets leading to Menaquinone-7 insufficiency. Either lack or deficiency of a given vitamin invites multiple pathologies, some mild some severe, some experiential some silent, some acute some chronic. Until this knowledge is available to an individual, he is likely to consider multiple healing effects of a vitamin as panacea. Researchers have now realized that most of the global population is facing multiple severe morbidities due to lack of or inadequate levels of Menaquinone-7 in diet and supplementation. The "Next Big Thing" in medicine is Menaquinone-7 with what the science has revealed already. This vitamin will advance on an exponential curve.

## Conflict of interest

Dr. Dilip S. Mehta, Dr. Anselm de Souza, and Dr. Shashank S. Jadhav are CEO, Managing Director and Medical Director of Synergia Life Sciences Pvt. Ltd.

## Author details

Dilip Mehta, Anselm de Souza and Shashank S. Jadhav*
Synergia Life Sciences Pvt. Ltd., Mumbai, India

*Address all correspondence to: shashank@viridisbiopharma.com

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